

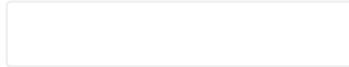


Session PO.BSB02.02 - Mathematical Modeling

5494 / 12 - How cancer arises from chronic inflammation, based on complexity theory

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Virtual Meeting II: E-Posters

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Disclosures

N.L. Pernick: None.

Abstract

Introduction: This paper discusses how cancer arises from chronic inflammation, based on complexity theory.

Methods: We reviewed the medical literature to identify cancer types strongly associated with chronic inflammation. We then classified the chronic inflammatory etiologies, determined general mechanisms through which they promote cancer and speculated on network changes involved in transforming cells from physiologic to cancer attractor states.

Results: Bacterial and viral infection are a common etiology of chronic inflammation associated cancer and cause 15% of cancer cases worldwide, predominantly *Helicobacter pylori*, human papillomavirus and hepatitis B and C virus. Other etiologies include parasitic infestations by *Opisthorchis viverrini*, *Clonorchis sinensis* and *Schistosoma haematobium*; autoimmunity in Hashimoto thyroiditis, Sjögren syndrome and celiac disease; local trauma due to gastroesophageal reflux and hot beverages; excess weight; diabetes; Western diet (high fat, low fiber, low consumption of fruit and vegetables); aging and immune system dysfunction. General mechanisms include immune system activation that damages DNA by producing reactive oxygen and nitrogen species and nitrosamines; tumor immune evasion via immune suppression and immune senescence; antigen driven lymphoproliferation; continuous mitotic activity due to repair; synergy with other chronic stressors; creation of a tumor nurturing microenvironment; development of a "runaway" immune system; and microbiome changes that produce carcinogens or activate inflammation. Immune system dysfunction and germ line variations of inflammatory mediators can promote each step. From a network perspective, the usual physiologic state for many cellular processes consists of a delicate balance between stimulating and dampening forces, maintained by inherent network features and evolved control systems. Chronic inflammation may disturb this balance, leading to propagation of network instability throughout the cell, across adjacent tissues and ultimately systemically. This may create identifiable network hierarchies and intermediate states (hyperplasia, metaplasia or dysplasia), but some changes in network and molecular patterns may not alter histology. Ultimately, cells may move to a cancer attractor state.

Summary: Chronic inflammation causes cancer by initiating local changes to cellular networks and their microenvironment which facilitate their escape from physiologic states towards intermediate and cancer attractor states. This suggests that early detection and reduction of these inflammatory changes may reduce cancer mortality. Novel treatment options include more diverse treatment combinations, destabilizing existing cancer attractors and their microenvironment, stimulating physiologic pathways that stabilize networks, reducing other chronic stressors and optimizing rational medical care.